Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2025-2026

Conference #1 — 20 August 2025

CASE I:

Signalment:
Equine Standardbred. Female, 2 days.

History:
Filly foal born with angular limb deformities of the all limbs, worse in the hind limbs. Foal had a fever, leukocytosis and neutrophilia.

Gross Pathology:
The crown rump length of this foal was 112 cm, Bilaterally, the tarsal joints were fixed in extension. The left fetlock has a 15 degree lateral deviation. The right tarsus was deviated about 30% and the fetlock a further 15 degrees medially. Eponychia were on all 4 hooves. The thyroid was normal in appearance. Bone marrow appeared to be normal also.

Laboratory Results:
Leukocytosis, neutrophilia, hypoproteinemia, hypoalbuminemia, severe hypoglobulinemia, azotemia, increased bilirubin, cholesterol, GLDH, Alk Phos, and CK.

Microscopic Description:
About 20% of follicles have colloid in the lumen and even those had a small diameter. The majority of follicles have no colloid or lumens. The thyroid follicular cells are tall cuboidal to columnar with abundant cytoplasm. Thyroid medullary cells are inapparent.

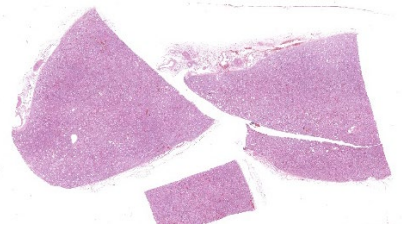

Figure 1-1: Thyroid gland, foal. Multiple sections of thyroid gland are submitted for examination. A few ectatic follicles are visible at subgross examination. (HE, 5X)

Contributor's Morphologic Diagnoses:
Thyroid follicular cell hypertrophy and hyperplasia, with minimal colloid.

Contributor's Comment:
This foal has the macroscopic and microscopic changes of the syndrome of horses known as thyroid hyperplasia and musculoskeletal deformities (TH-MSD) or congenital hypothyroidism-dysmaturity syndrome. Foals with or without musculoskeletal deformities may have microscopic thyroid hyperplasia yet no clinically visible goitre. A variety of musculoskeletal deformities occur.

Affected horses are newborn or are aborted. Foals have microscopic hyperplasia of the thyroid gland and may have multiple congenital musculoskeletal deformities. The thyroid gland are usually of normal size macroscopically.

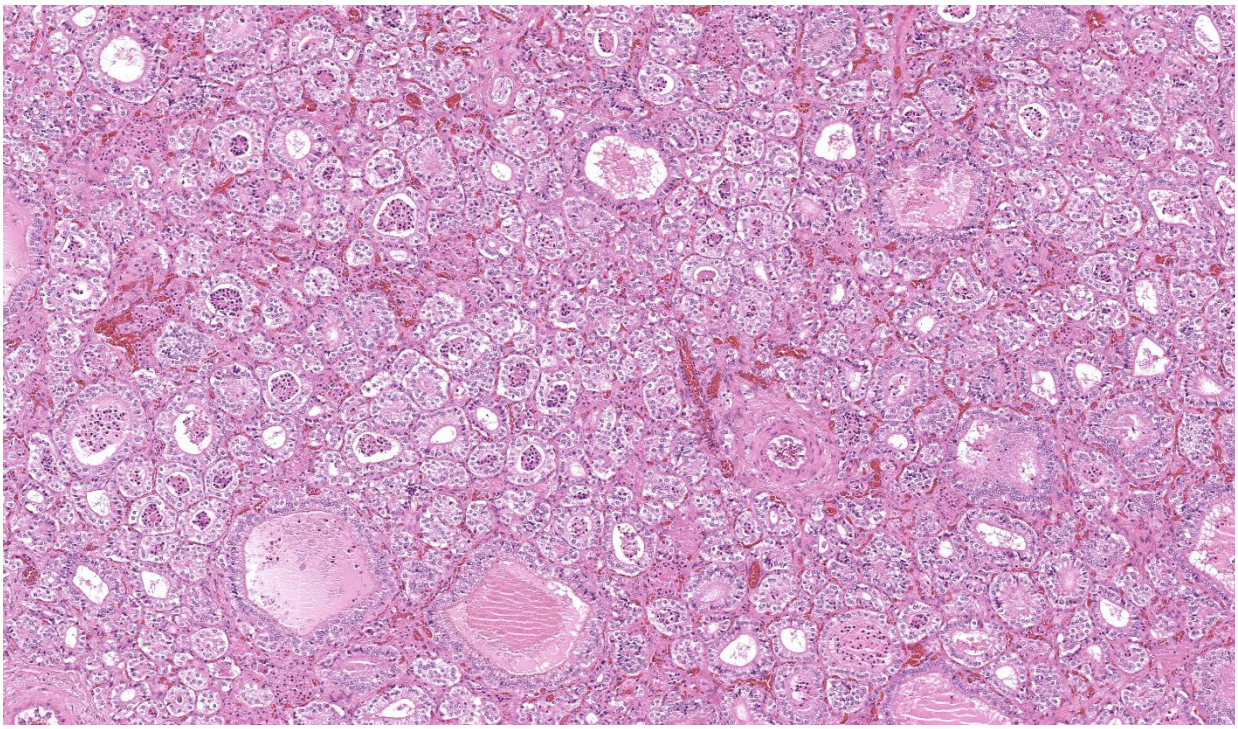

Figure 1-2: Thyroid gland, foal. There is wide variation in the size of follicles. Some are collapsed, some are dilated up to 0.2mm. Few have any colloid. (HE, 136X)

Musculoskeletal lesions include mandibular prognathia, inappropriately ossified carpal and tarsal bones, flexural deformities of the forelimbs and ruptured tendons of the common digital extensor muscles. Foals have either normal or lengthened gestation, and they show signs of immaturity including a short soft coat and lax joints. Aborted foals may have osteopetrosis. It is attributed to micronutrient deficiency including iodine deficiency of the mare. Cases were initially reported in Western Canada but have been found in a variety of other locations in Canada and internationally including Europe. Unless the thyroid gland is examined histologically, the diagnosis will be missed.

Contributing Institution:
Department of Pathobiology, Ontario Veterinary College, University of Guelph

JPC Diagnoses:
Thyroid gland: Follicular hyperplasia,diffuse, marked.

JPC Comment:
And…they're off! Conference is breaking out of the starting gate of the 2025-2026 Wednesday Slide Conference with an equine-centric lineup moderated by the Director of the Joint Pathology Center, COL Sherri Daye. This first case stimulated excellent discussion of a syndrome that is making its debut appearance in the WSC. There have been some great cases of goiter over the years (most recently, WSC 2017-2018, Conf 19, Case 4), but never an equine thyroid hyperplasia and musculoskeletal dysmaturity syndrome (THMSD). Many thanks to the contributor for this unique case. Conference discussion was based largely around the pathogenesis of this condition and potential causes of iodine imbalance in pregnant mares, including consumption of too much or too little iodine or the ingestion of goitrogenic plants (Brassica spp, clover, soybeans, sorghum, etc.). The lack of thyroid C-

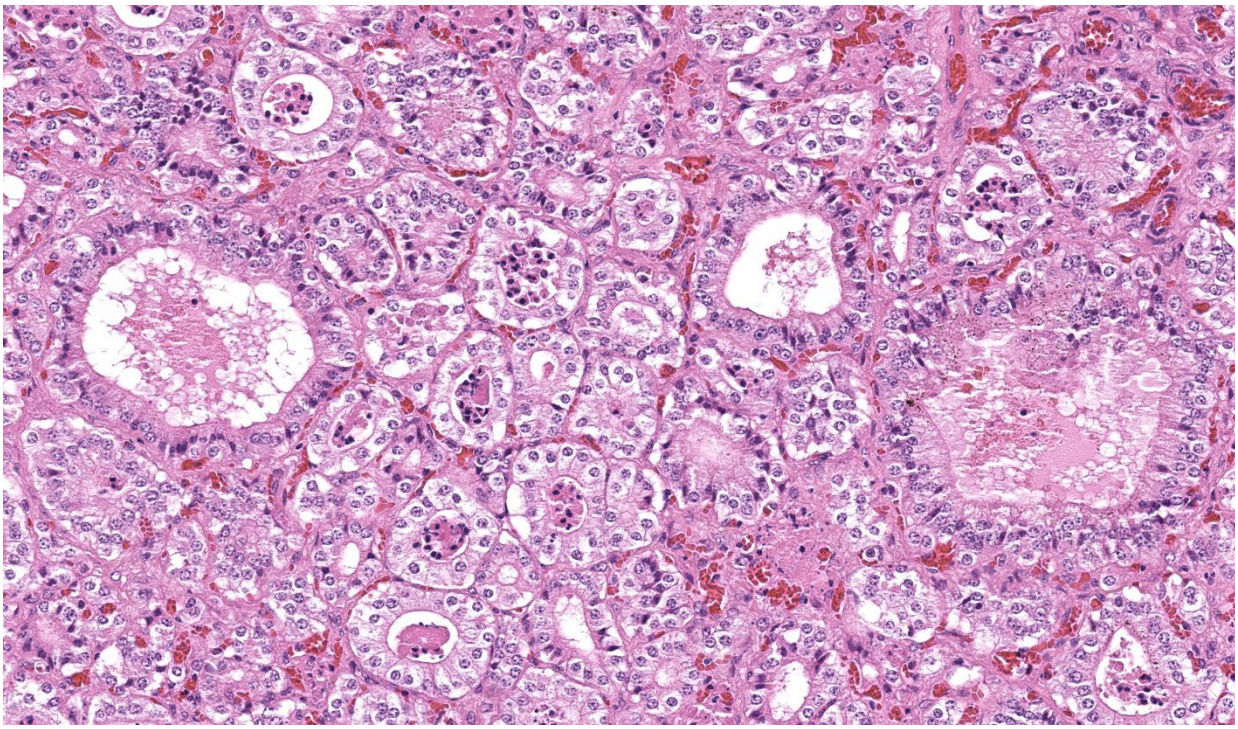

Figure 1-3: Thyroid gland, foal. Follicles are lined by a single layer of hypertrophiccolumnar epithelium. Few follicles contain any colloid. In numerous follicles, the follicular epithelium is apoptotic and sloughed into the lumen. There are few totally collapsed and necrotic follicles and a single ectatic follicle at right. (HE, 381X)

cells in this condition provided a good exercise for participants in evaluating what is not present and how that is often just as important as seeing what is.

Equine THMSD was first described in 1981 in Western Canada when 7 foals were submitted to the Western College of Veterinary Medicine for numerous musculoskeletal deformities, where it was determined that all foals also had evident goiter. Since these cases were reported, this syndrome has been described in thousands of foals across Canada, Europe, and the United States. As the contributor stated, many of the foals affected by this syndrome have grossly normal thyroid glands and a range of congenital deformities of variable severity, but all have had histologic evidence of thyroid hyperplasia. Although no exact cause has been decided on, the most widely accepted risk factors include nutritional iodine deficiency and/or high dietary nitrate in the dam leading to the congenital changes in the fetus. In humans, low selenium can also contribute to the development of a similar condition4. Ensuring adequate nutrition of the dam throughout pregnancy is the best prevention. You know what people say…an ounce of a balanced diet is worth of a pound of appropriately functioning thyroids…or something like that.

A quick review of thyroid physiology is warranted to understand the proposed pathogenesis of THMSD. The thyroid gland is responsible for several physiologic functions, including metabolism, thermogenesis, gluconeogenesis, cardiovascular support, neuronal development, and musculoskeletal development. Thyroid hormone production starts with the hypothalamus, which produces thyrotropin-releasing hormone (TRH). TRH acts on the anterior pituitary to stimulate release of thyroid-stimulating hormone (TSH), which is the major regulator of thyroid hormone synthesis in the thyroid gland. These three organs make

up the hypothalamic-pituitary-thyroid axis, which allows for negative feedback control of thyroid hormone production. When functioning appropriately, the thyroid gland produces thyroxine (T4) and triiodothyronine (T3), with T3 being the bioactive form. Although low levels of T3 are produced directly, most T3 must be converted within the target cell from T4. That's where the iodine comes in, because conversion of T4 to T3 requires iodine! When there is a lack of iodine, there will not enough bioavailable thyroid hormone being produced. In cases of low thyroid hormone levels, TSH will continue to be produced by the anterior pituitary to stimulate the thyroid glands to produce thyroid hormone. This results in hyperplasia of the thyroid gland, which can become severe enough to cause goiter.

How does this tie in to the musculoskeletal deformities? Thyroid hormone is a critical regulator of energy availability and consumption within the musculoskeletal system6. While the hypothalamus has mostly thyroid hormone receptor (TR) β, TRα is the main receptor expressed in the skeleton and mediates T3 action in bone and cartilage7. Chondrocytes and osteoblasts are directly responsive to thyroid hormone and osteoclastic activity is sensitive to changes in thyroid hormone availability. It's not whether osteoclasts are direct target cells of T3 or if the effects on bone resorption are indirect and mediated by primary thyroid hormone actions in other cells7. Via its action on these cells of the skeleton, thyroid hormone works to regulate intramembranous and endochondral ossification, control the rate of linear growth and bone maturation, and ensure appropriate skeletal mineralization. In an absence of thyroid hormone, these processes are delayed, which can result in the variety of dysmaturities seen in THMSD-affected foals._.

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CASE II:

Signalment:

19-year-old, American miniature stallion.

History:

The horse presented with a 24-hour history of lethargy and possible neurologic signs. Circling to the left had been noted the day prior to admission, and the horse was frequently seen standing quietly with his head lowered. During physical examination, the horse was quiet, yet alert and responsive. A cranial nerve exam was within normal limits. quiet,

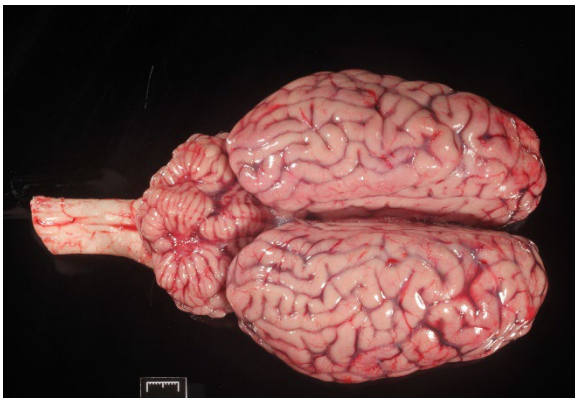

Figure 2-1: Brain, horse. The right frontal lobe is assymetrically enlarged. (Photo courtesy of: Department of Veterinary Pathobiology, College of Veterinary Medicine, Texas A&M University, https://vtpb.tamu.edu).

yet alert and responsive. A cranial nerve exam was within normal limits. Blood work, including bile acids and ammonia levels, was unremarkable as were cervical spinal radiographs. The horse was treated with flunixin meglumine, Vitamin E, Marquis®, and intramuscular dexamethasone injections. Despite treatment for 4 days, the horse developed an intermittently absent menace of the left eye, a left head tilt, compulsive walking in the right direction, and a medial strabismus of the left eye. These signs progressed to full body muscle fasciculations, fixed dilated pupils, absent pupillary light reflex and menace bilaterally, head pressing, of the left eye. These signs progressed to full body muscle fasciculations, fixed dilated pupils, absent pupillary light reflex and menace bilaterally, head pressing, and a rising body temperature. Due to the horse's worsening condition, humane euthanasia was elected.

Gross Pathology:

The right frontal lobe was slightly enlarged (asymmetry) (Fig.1). On cut surface, the white matter was mildy expanded and yellow (edema). A 1.1x0.5 cm, soft, red-brown area was within the right thalamus (malacia).

Laboratory Results:

Rabies fluorescent antibody testing: negative; Eastern Equine Encephalitis virus RT-PCR: negative; Western Equine Encephalitis virus RT-PCR: negative; West Nile virus RT-PCR: negative; St. Louis Encephalitis virus RT-PCR: negative.
(https://tvmdl.tamu.edu/tests/panfungal-pcr/)

Panfungal PCR targeting the internal transcribed spacer (ITS) region and agarose gel electrophoresis yielded 2 bands of DNA at approximately 350bp and 450bp. DNA was purified from the gel and sequenced. The resulting 119bp and 295bp sequences were analyzed with the NCBI BLAST database. The sequence matched *Chaetomium strumarium* and *Malassezia restricta* with 100% identity.

Microscopic Description:

Cerebrum: Multifocally and randomly infiltrating the neuroparenchyma are numerous distinct accumulations of inflammatory cells composed of epithelioid macrophages and neutrophils with fewer lymphocytes, multinucleated giant cells (Langhans and foreign body type), and plasma cells. Inflammatory cells also frequently and moderately expand

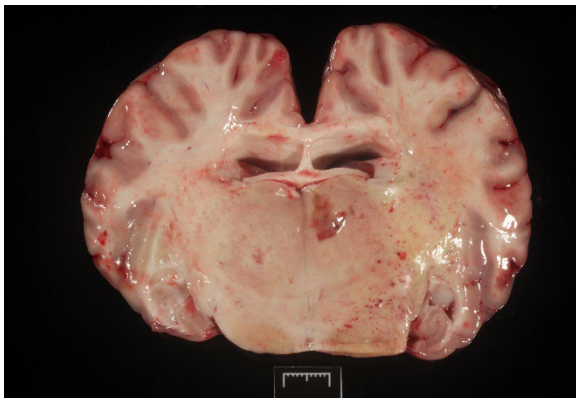

Figure 2-2 Brain, horse. A 1.1x0.5 cm, soft, red-brown area of malacia is present within the right thalamus . (Photo courtesy of: Department of Veterinary Pathobiology, College of Veterinary Medicine, Texas A&M University, https://vtpb.tamu.edu).

Virchow-Robins' spaces. Admixed extracellularly with inflammatory cells and phagocytosed within macrophages and multinucleated giant cells are sections of golden-brown, 7-10 µm pigmented fungal hyphae characterized by frequent septation, dichotomous branching, and terminal bulbous swellings. The section also exhibits multifocal areas of cavitation with loss of neuroparenchyma and replacement by numerous foamy macrophages (gitter cells) accompanied by increased numbers of astrocytes and microglia (gliosis) with increased clear space (edema) and areas of hemorrhage. Neurons in these areas are multifocally shrunken and hypereosinophilic with pyknotic nuclei (necrosis) and axons are frequently swollen and hypereosinophilic and surrounded by dilated myelin sheaths (spheroids).

Contributor's Morphologic Diagnoses:
Cerebrum: Marked, multifocal to coalescing, chronic, pyogranulomatous encephalitis with extracellular and intrahistiocytic fungal hyphae.

Contributor's Comment:
Histologic evaluation identified fungal encephalitis as the cause of the horse's neurologic signs with PCR results identifying the dematiaceous fungus, *Chaetomium sp.*, as the cause. Meningoencephalitis associated with dematiaceous fungi has been previously described in horses[10].

The term "dematiaceous" has been used to describe fungi that are olivaceous, dark brown, or black due to the presence of melanin or melanin-like pigment within the cellular walls13. It has been suggested that the term "dematiaceous" is not appropriate given its etymologic derivation from the Greek "deme," meaning "bundle." The term "melanized" has been used more recently to describe pigmented fungi[11]. Melanized fungi are responsible for causing a wide range of diseases including

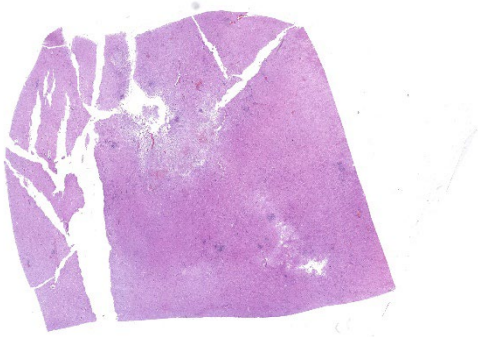

Figure 2-3: Cerebrum, horse: One section of cerebrum is submitted for examination. There are multifocal to coalescing areas of necrosis within this section, and cuffed vessels are visible at the periphery. (HE, 10X)

chromoblastomycosis and phaeohyphomycosis. Chromoblastomycosis is a chronic infection of the skin and subcutaneous tissues, characterized by muriform bodies or sclerotic bodies, and typically caused by *Fonsecaea pedrosoi, Fonsecaea compacta, Phialophora verrucosa,* or *Cladosporium carrionii*[13].

The name "phaeohyphomycosis" is derived from the Greek word "phaeo" meaning "dusky" or "grey." In phaeohyphomycosis, the tissue morphology of the fungus is predominantly composed of hyphae (mycelial). Although the agents of phaeohyphomycosis may exhibit a dark coloration in culture and the gross appearance of these lesions may be partially pigmented, these organisms appear non-pigmented in histologic sections stained with using H&E. In such cases, Fontana-Masson may be helpful in identifying the pigmented hyphae, while Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) usually obscure the pigment[13].

In humans, phaeohyphomycosis causes opportunistic infections in the cornea, sinus, skin, and lungs of immunocompromised patients, with the exception of central nervous system infections, which tend to affect immunocompetent individuals. Genera involved with phaeohyphomycosis in humans include: *Alternaria, Bipolaris, Chaetomium, Clado-*

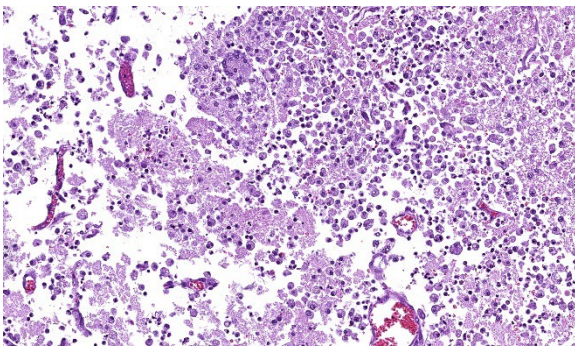

Figure 2-4: Cerebrum, horse. Areas of necrosis contain numerous Gitter cells, viable and necrotic neutrophils, rare multinucleated foreign body giant cells, and in areas of neuroparenchymal loss, gliovascular strands (bottom left). (HE, 332X)

phialophora, Curvularia, Exophiala, Exserohilum, Lasiodiplodia, Lecythophora, Ochroconis, Phaeoacremonium Pseudallescheria, Rhinocladiella, and *Scedosporium*, among others[13].

Fungi of the members of the orders Chaetothyriales, Pleosporales, Ochroconiales, and Capnodiales are involved in phaeohyphomycosis in a wide range of cold-blooded vertebrates, such as crustaceans, captive and farmed fish, amphibians, and aquarium animals. Phaeohyphomycosis is less prevalent or less recognized in warm-blooded animals[12]. Cats appear to be more susceptible with case reports of this infection documenting nasal, renal, cutaneous, subcutaneous, ocular, cerebellar and systemic involvement[12,14]. Members of the family Chaetomiaceae are ubiquitous fungi which reside in soil enriched with manure or cellulosis-decaying materials[1,2]. A certain prevalence of chaetomium-like species was noted in desert soil subjected to conditions of dryness and extremely variable temperatures[2]. *Chaetomium atrobrunneum*, *C. perlucidum*, and *C. strumarium* are neurotropic species causing serious and life-threatening infections in people[1,3].

Mycotic encephalitis is rare in horses. Reported cases include aspergillosis[4], one of which presented with concurrent Mucor sp. infection, and cryptococcosis. Recently, phaeohyphomycosis within the Chaetomiaceae family, including *Acrophialophora fusispora*, *Acrophialophora levis*, and *Chaetomium strumarium* has been described as novel causes of equine neurotropic mycosis. Affected animals ranged from 8 to 22 years of age. The most common central nervous system location was the cerebrum[10].

Panfungal PCR on formalin-fixed paraffin-embedded (FFPE) tissues targeting the ribosomal RNA large subunit coding region and the noncoding internal transcribed spacer-2 region is a useful technique when fresh tissue is not available for culture. Although pigmented fungi may appear to be a straightforward identification on H&E sections, variability exists in the amount of melanin produced by a genotypic variant, and thus these fungi could be confused with other hyaline hyphae. Additionally, pigmented fungi cannot be identified to the genus level using histologic evaluation alone[5]. In this case, the amplified *Malassezia restricta* sequence is a common contaminant in paraffin blocks and unrelated to the cause of the fungal infection in this case. Panfungal PCR and sequencing results should always be correlated with the assessment of fungal morphology.

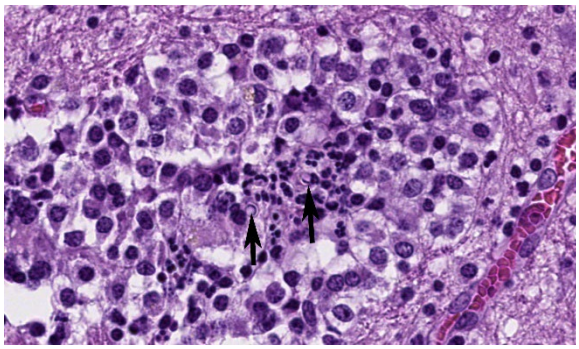

Figure 2-5: Cerebrum, horse. Fungal hyphae are difficult to visualize on HE section. Cross sections of hyphae may be seen within foreign body-type giant cell macrophages. (HE, 526X)

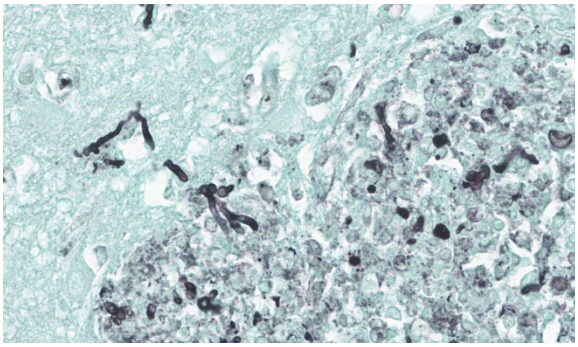

Figure 2-6: Cerebrum, horse. A silver stain demonstrates the morphology of the fungal hyphae with elongate 4-10um pauciseptate hyphae. (GMS 600X)

Contributing Institution:
Department of Veterinary Pathobiology
College of Veterinary Medicine and Biomedical Sciences, Texas A&M University
https://vtpb.tamu.edu

JPC Diagnoses:
Cerebrum: Encephalitis, necrotizing and pyogranulomatous, focally extensive, severe, with vasculitis and rare pigmented fungal hyphae.

JPC Comment:
This is a excellent case of a fungal encephalitis in a horse caused by a unique mycotic pathogen. The contributor gives a thorough overview of this condition and other relevant fungi in their comment. While it is well-established that the brain and retina of horses, as well as the nervous system and skin of cats, are frequent targets of dematiaceous fungi in veterinary species, this particular pathogen is rarely isolated from infections in animals.

This conference case stimulated discussion on how, despite the challenge of finding the hyphae on the H&E slide, the type of inflammation (pyogranulomatous) should make the pathologist suspicious for particular types of pathogens and stimulate careful search in affected areas for those agents. A GMS stain readily revealed the fungal hyphae within the affected neuropil and was shown to conference participants following the H&E description. A great review of microglia and their roles followed case presentation, including the differences between resting microglia, gitter cells, multinucleated giant cells, and "rod" cells. A brief review of the necessary fungal features to mention in a slide description was covered and included: size, branching (acute vs right angle, dichotomous vs irregular, and frequency), parallel vs. non-parallel walls, septation, pigmented or non-pigmented, and mention of whether the fungus is angioinvasive or not. One conference participant also made an excellent point that, after others questioned the pigmentation of the fungi outside of that seen in histiocytes, that pigmented fungi are classified as such based on their appearance on a growth plate and not on an H&E slide.

A closer look at *Chaetomium* sp fungi helps elucidate how they cause illness. *Chaetomium* sp are well-documented neurotropic fungal pathogens of humans, but until recently, were not associated with disease in veterinary species11. "Chaeto-" comes from the Greek word "chaitē", meaning "long hair" in reference to the filamentous setae covering the fruiting bodies of these fungi. These setae are considered one of the defining morphologic features of this fungal genus, and differing setae characteristics within the genus can assist in speciation.

These opportunistic fungi, when in an environment that enables their growth, produce a variety of mycotoxins, including several types of chaetoglobosins. Chaetoglobosins are a type of cytochalasin fungal metabolite that binds to and prevents the polymerization of actin filaments in animal cells, inhibiting cellular movement, changing cellular morphology, and hindering mitosis, ultimately resulting in apoptosis of the affected cell[5]. Chaetoglobosin A, in particular, is highly toxic to

mammalian cells and, even at low doses, has been demonstrated to be acutely fatal in laboratory rats and mice[9]. Other produced toxins, such as chaetoviridins, have antimicrobial and antifungal properties against other fungi, enabling the *Chaetomium* sp to thrive while inhibiting the growth of competitors[4].

Chaetoviridins have also been shown to inhibit tumor development in carcinogenic mice models via targeted cytotoxic effects. As such, chaetoglobosins and chaetoviridins are currently being studied for their use as potential antimicrobial and chemotherapeutic agents6. *Chaetomiaciae* sp are yet another excellent example of the natural world enabling biochemists and pharmacologists to walk the fine line between therapeutic dosage and toxicity.

References:

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CASE III:

Signalment:
10 yr Gypsy Vanner mare, *Equus caballus*, horse.

History:
Tissue from a 10-year-old Gypsy Vanner mare with a 24-hour history of colic. On presentation, the horse was tachycardic with decreased borborygmi in all quadrants. An abdominal ultrasound was performed that identified increased motility on the right side, decreased motility on the left side, and severely thickened sections of intestine. An abdominocentesis found increased lactate (4.0 mmol/L). Peripheral lactate was in the normal range (1.5 mmol/L). The mare was taken into surgery where a focal area of thickened small colon was identified, and a resection and anastomosis was performed along with biopsy of the affected site. Ultimately the mare did poorly following surgery, and was euthanized; a postmortem examination was not performed, and examination was limited to biopsy tissues removed during surgery.

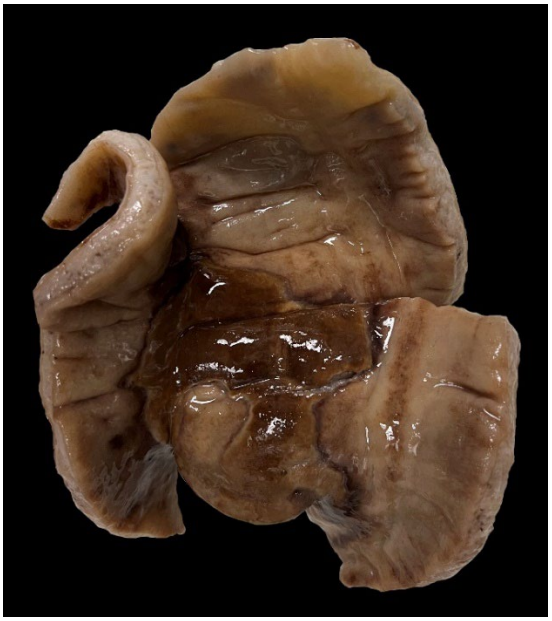

Figure 3-1: Colon, horse. A segment of opened small colon was submitted for histologic evaluation. On the mucosal surface, there is a focal, well demarcated, irregularly marginated tan to brown plaque rimmed in dark red that measures 8x9cm. (Photo courtesy of: The Ohio State University College of Veterinary Medicine, Department of Veterinary Biosciences, https://vet.osu.edu/biosciences).

Gross Pathology:
A segment of opened small colon measuring 16cm in length and 17cm in width was submitted for histologic evaluation. The segment is 1cm thick on the margins, narrowing to 0.4cm thick in the center of the section. On the mucosal surface, there is a focal, well demarcated, irregularly marginated tan to brown plaque rimmed in dark red that measures 8x9cm.

Laboratory Results:
Peripheral lactate: 1.5 mmol/L
Abdominal effusion lactate: 4.0 mmol/L

Microscopic Description:
Small colon: Markedly, transmurally expanding the bowel wall, with the submucosa and muscularis layers most prominently affected, are numerous eosinophils, macrophages, and fewer lymphocytes, plasma cells, and neutrophils. The mucosa is mildly expanded by described inflammatory infiltrates, and vessels within the mucosa are congested with multifocal, variably minimal to moderate numbers of extravasated red blood cells (hemorrhage). Segmentally, approximately 50% of the mucosa has relatively sharply-demarcated loss of differential staining with variable retention of

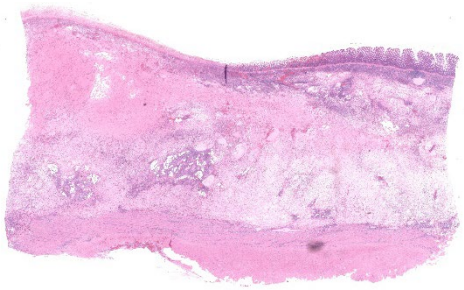

Figure 3-2: Colon, horse. One section of severely inflamed colon is submitted for wzmination. At subgross, mucosal necrosis (top left) and marked expansión of the submucosa are evident (HE, 10X)

cellular architecture (coagulative necrosis) in termixed with foci comprised of karyorrhectic nuclear debris and granular eosinophilic material (lytic necrosis). Necrosis extends regionally into the superficial underlying submucosa. Beyond described inflammatory cells, the submucosa is further severely expanded by abundant homogenous pale eosinophilic fluid (edema), resulting in the submucosa comprising approximately 70% of the entire thickness of the bowel wall. Within the tunica muscularis, described inflammatory cells infiltrate between and separate branching bundles of smooth muscle, often loosely associated with small caliber vessels lined by hypertrophied endothelial cells. Within both the submucosa and muscularis, inflammatory cells are multifocally accompanied by mild proliferation of plump spindle cells (fibroblasts). The serosa is mildly affected by inflammation with associated multifocal vascular congestion and patchy hemorrhage. Grocott methenamine silver (GMS) stain is performed on tissues, and no etiologic agents are identified.

Contributor's Morphologic Diagnoses:
Small Colon: Marked, multifocal to coalescing, subacute, submucosal and tunica muscularis-focused, eosinophilic, histiocytic, and neutrophilic colitis with marked diffuse edema and regional acute necrosis

Contributor's Comment:
The key histologic findings in this lesion are 1) the marked transmural infiltration of eosinophils within the segment of thickened bowel and 2) the particular concentration of eosinophils within the submucosa and muscularis of the affected bowel. In the horse, scattered eosinophils are commonly found within normal tissues of the gastrointestinal tract, but recruitment of eosinophils in diseased states are less common and most frequently attributed to parasitic migration, pythiosis, type I hypersensitivity, or idiopathic inflammatory conditions[10,17]. The eosinophilic inflammatory conditions with unknown causes have been categorized as part of an inflammatory bowel disease (IBD) complex[14]. Two distinct idiopathic causes will be discussed in detail: idiopathic focal eosinophilic enteritis (IFEE) and chronic eosinophilic enteritis (part of the multisystemic epitheliotropic eosinophilic disease, MEED). Idiopathic eosinophilic enterocolitis, or diffuse eosinophilic enteritis as proposed by Makinen *et al*., is a third idiopathic condition grouped into the IBD complex that is localized to the alimentary tract and consists of diffuse infiltrates of eosinophils with fewer macrophages than IFEE lesions and no obstructive disease, but with an otherwise similar histologic appearance[2,9,14,17].

IFEE was first identified in the early 1990s and since then has been documented in the United Kingdom, Republic of Ireland, United States and South Africa[1,12]. Archer *et al*. found IFEE to be an emerging disease with an increased incidence of cases from 2002 to 2010 in addition to possible seasonal and geographic correlations when cases are compared to control colic patients[1]. Clinical signs consist of acute colic, and focal circumferential thickening of the intestines can be identified on rectal palpation or by ultrasound[1]. The focal lesions are most often identified within the small intestine but have also been noted in the dorsal

left colon and can result in obstructive disease[4,12,16,17]. Surgical resection of the affected segments of bowel is thought to be curative[1,2]. Histologically, the lesions consist of focal infiltrations of eosinophils and macrophages within the submucosa and tunica muscularis with increased numbers of mononuclear cells[2,9,17]. The lamina propria is typically expanded with fewer eosinophils and abundant lymphocytes, plasma cells, and macrophages[2,9,17]. A causative agent has not been identified, but exposure to stagnant water has been a proposed contributor[1]. A type I hypersensitivity or parasitism cannot be ruled out given the nature of the disease.

Chronic eosinophilic enteritis has been documented in conjunction with MEED since the early 1980's[11,19]. Young horses are most at risk for developing the disease[14,18]. Clinical symptoms typically develop over a period of months with eosinophilic and granulomatous lesions noted most often in the skin, biliary ducts, pancreas, lung, salivary glands, and mesenteric lymph nodes[15,17]. Clinical presentation often consists of severe weight loss that develops over months and pitting edema attributed to enteric loss of plasma protein from chronic inflammation[3]. With colonic involvement, horses will develop diarrhea[17]. The intestinal histologic lesions consist of mucosaI, submucosal, and often transmural eosinophilic infiltrates accompanied by mast cells, macrophages, lymphocytes, and plasma cells[3,17,18]. In the author's experience, this will often include formation of discrete eosinophilic granulomas, which is in contrast to IFEE. Often lesions will contain extensive fibrosis, villous atrophy, and muscularis mucosa hypertrophy[17]. Proposed pathogeneses include a type I hypersensitivity to migration of enteric parasite larva or ingested allergens, or undetected IL-5 secreting T-cell lymphoma as supported by a documented case of CD3+ intestinal lymphosarcoma with concurrent MEED in the horse[8,17].

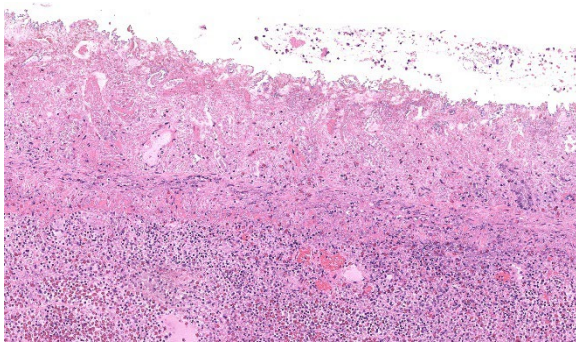

Figure 3-3: Colon, horse. There is segmental necrosis of the colonic mucosa; necrosis extends into the underlying muscularis mucosae. (HE, 215X)

In other species, eosinophilic enterocolitis entities attributed to a variety of causes has been identified in humans, dogs, cats, ferrets, and cattle either alone or with multisystemic inflammation[5,6,7,13].

Collectively, while occurring in an unreported location (small colon), the clinical presentation, gross finding of focal thickening of the bowel, and histologic appearance of this case support a diagnosis of IFEE. Histologically, there is extensive submucosal and tunica muscularis infiltration by predominantly eosinophils and macrophages, with fewer numbers of neutrophils, lymphocytes, plasma cells. While neutrophils are not commonly described in IFEE lesions, we attribute the presence of neutrophils to regional necrosis of the bowel, which we suspect is secondary to obstruction. The concentration of inflammatory cells within the submucosa and muscularis is reportedly a key feature of IFEE, supporting this diagnosis. The differential diagnosis of chronic eosinophilic enteritis as a component of MEED is not favored in this case due to the absence of eosinophilic granulomas, lesion distribution in the bowel wall, and absence of other known affected systems, although lack of postmortem examination precludes true evaluation of the latter point. Lastly, idiopathic eosinophilic enterocolitis/diffuse eosinophilic enteritis is not favored in this case due to the focal and obstructive nature of the le-

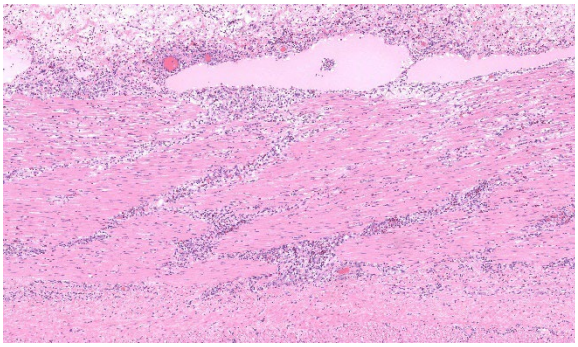

Figure 3-5: Colon, horse. The mixed inflamamtion extends from the dematous submucosa down into the muscularis, infiltrating along perivascular áreas and between muscle fibers. (HE, 115X)

sion, as well as the abundance of macrophages. Despite our preference for this lesion representing IFEE, we recognize that these conditions are not extensively characterized within veterinary pathology literature, so we cannot fully rule out that this lesion may reflect a variant of one of these other idiopathic conditions. In this case, infectious agents (i.e. fungal or fungal-like organisms, e.g. *Pythium* spp.) were not identified via H&E and GMS evaluation, but we cannot rule out that undetected agents may be inciting this lesion. Overall, this case highlights the need for further investigation and characterization of equine idiopathic eosinophilic inflammatory bowel conditions.

Contributing Institution:
The Ohio State University College of Veterinary Medicine, Department of Veterinary Biosciences
https://vet.osu.edu/biosciences

JPC Diagnoses:
Colon: Colitis, eosinophilic, subacute, focally extensive and transmural, severe, with segmental necrosis and marked edema.

JPC Comment:
The contributor provided a thorough comment comparing two entities that share many similarities yet have some distinct differences. Conference discussion was largely centered around comparing idiopathic focal eosinophilic enteritis (IFEE) and multisystemic epitheliotropic eosinophilic disease (MEED), with the clearest differences being the distribution of lesions and histologic presence of eosinophilic granulomas in MEED. However, it was also stated that the lack of eosinophilic granulomas does not rule out MEED and attention should be given more so to distribution and clinical history due to the similarities in these conditions. There was also special attention given to the segmental coagulative necrosis in this case, which conference participants largely attributed to the histologically evident vasculitis. Ultimately, in light of the clinical and histologic findings in this case, conference participants agreed with the contributor's diagnosis of IFEE. Grocott's methenamine silver (GMS) and periodic acid-Schiff (PAS) stains were run on this case and did not reveal any infectious agents, which is consistent with what the contributor reported in their own work-up.

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CASE IV:

Signalment:
5-year-old, intact male, Criollo horse (Equus caballus)

History:
The horse had a 3-day history of progressive

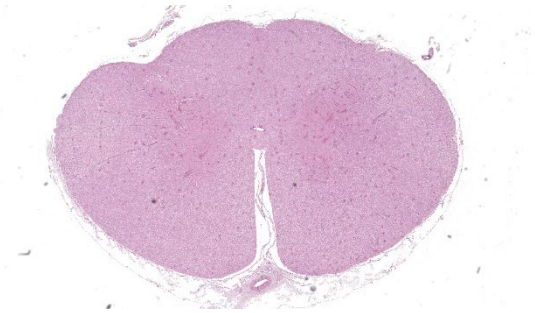

Figure 4-1: Cervical spinal cord, horse. A section of cervical spinal cord is submitted for examination. At this magnification, small foci of hemorrhage are visible throughout the gray and white matter. (HE, 10X).

neurological signs including lethargy, circling, recumbency, paralysis, and occasional seizures, and was humanely euthanized due to severe clinical deterioration and poor prognosis.

Gross Pathology:
Gross findings included flattening of gyri in the cerebral hemispheres, diffuse hyperemia of the cerebral leptomeninges, and scattered foci of hemorrhage in the gray matter of the spinal cord.

Laboratory Results:
Samples of brain and spinal cord were positive for Western equine encephalitis virus (WEEV) by RT-PCR.

Microscopic Description:
Spinal cord (C1): multifocally the perivascular spaces are expanded and infiltrated by lymphocytes, histiocytes and fewer plasma cells forming layers of up to 7 cell thick (perivascular cuffing), with occasional accumulation of perivascular eosinophilic homogeneous finely granular material (protein-rich edema fluid. Similar inflammatory cells multifocally infiltrate the adjacent neuropil and/or white matter, occasionally forming discrete nodular aggregates. Rarely, multinucleated cells with abundant eosinophilic cytoplasm (interpreted as multinucleated astrocytes) are admixed with the inflammatory infiltrates. There is mild to moderate erythrocyte extravasation into the neuroparenchyma (hemorrhage). The inflammation, edema and hemorrhages are more frequent and severe in the gray than the white matter, with hemorrhages being particularly prominent in the dorsal horns. Scattered neurons depict chromatolysis (neuronal necrosis) and are either surrounded by inflammatory/glial cells (satellitosis) or invaded by them (neuronophagia) (not present in all sections). Capillaries are frequently hyperemic and lined by plump endothelial cells. Few swollen axons within dilated myelin sheaths (spheroids) are observed in the white matter. The leptomeninges are multifocally infiltrated by lymphocytes, histiocytes and fewer plasma cells.

Contributor's Morphologic Diagnoses:
Spinal cord (C1): Meningomyelitis, lymphocytic, histiocytic and plasmacytic, multifocal, moderate, with neuronal necrosis and hemorrhage, horse.

Contributor's Comment:
Differential diagnoses for non-suppurative

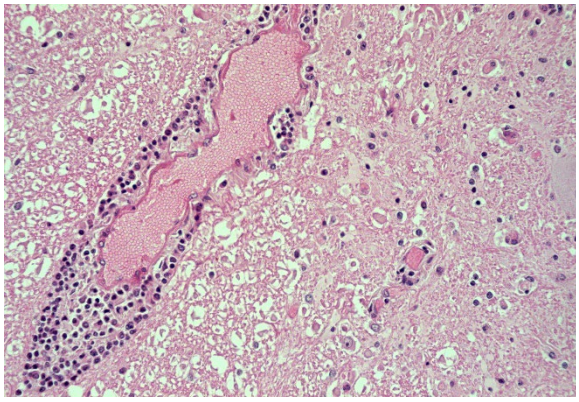

Figure 4-2: Cervical spinal cord, horse: Infiltration of lymphocytes, histiocytes and plasma cells in the perivascular space of a venule located in the junction between the white and gray matter. (HE, 400X). (Photo courtesy of: Instituto Nacional de Investigació Agropecuaria (INIA), La Estanzuela, Uruguay. www.inia.uy)

encephalitis/encephalomyelitis in horses include viruses [neuropathogenic strains of Equine herpesvirus 1 (EHV 1), rabies virus, several viruses in the Flavivirus genus such as West Nile virus (WNV), Japanese encephalitis virus (JEV), Saint Luis encephalitis virus (SLEV), and alphaviruses (Eastern, Western and Venezuelan equine encephalitis viruses: EEEV, WEEV and VEEV, respectively)], as well as protozoal diseases (Sarcocystis neurona, Neospora hughesi)[4,9,10,15].

Given that most viral causes of encephalitis in horses are zoonotic and/or notifiable to the World Organization for Animal Health, rapid confirmation of the etiologic diagnosis is crucial. This can be achieved by PCR, immunohistochemistry, or in situ hybridization targeting specifically the different viruses, by virus isolation, next generation sequencing, and/or by fluorescent antibody testing in the case of rabies.

While JEV is exotic in South America, neuropathic EHV 1, WNV, SLEV, WEEV, EEEV, and rabies are endemic or sporadically reported[1,5,6,11-13]. In the spring of 2023 and summer of 2024, a large epizootic outbreak of WEE affecting primarily horses and to a lesser extent humans occurred in South America, notably in Argentina,[16] Uruguay,[17] and southern Brazil[3]. The case presented here was the first equine case investigated in Uruguay during this epizootic in the summer of 2024. The epidemiological, clinical, and histopathologic findings lead to the suspicion of a viral encephalitis, and WEE was highly suspected as cases had recently been confirmed in neighboring areas of Argentina. WEEV was detected by reverse transcriptase PCR in samples of spinal cord and brain from this horse submitted to the

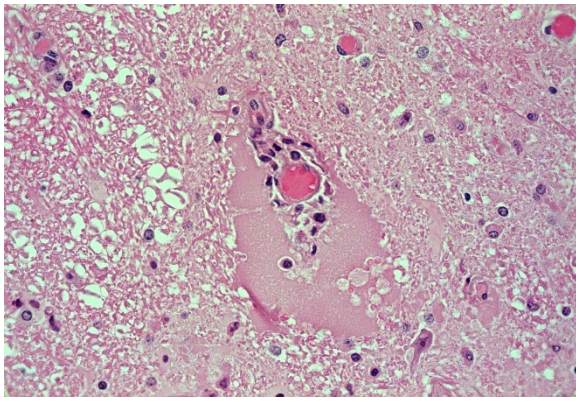

Figure 4-3: Cervical spinal cord, horse. The perivascular space of this capillary is infiltrated by a few lymphocytes and histiocytes and expanded by protein-rich edema fluid.

laboratory of the national sanitary authority ("Ministerio de Ganadería, Agricultura y Pesca" (MGAP), confirming the etiologic diagnosis.

Besides WEEV, VEEV and EEEV are other important alphaviruses (Togaviridae family), WEEV being the less virulent for horses of the three. Reservoir hosts are mainly birds (WEEV, EEEV), and rodents (VEEV)13. WEEV is transmitted primarily by *Culex* and *Aedes* mosquitoes from reservoir hosts to horses and humans, which are considered dead-end hosts.

The pathogenesis of alphavirus infection and encephalitis is complex and involves viremia after replication in peripheral tissues, neuroinvasion, and viral spread within the central nervous system. The initial viremia often goes unnoticed (subclinical), or manifests as fever and depression. If the animal fails to recover, neuroinvasion occurs, after which the virus replicates in neurons, glial cells, and blood vessels of the central nervous system. At this stage, the animal usually exhibits neurological clinical signs such as circling, cen

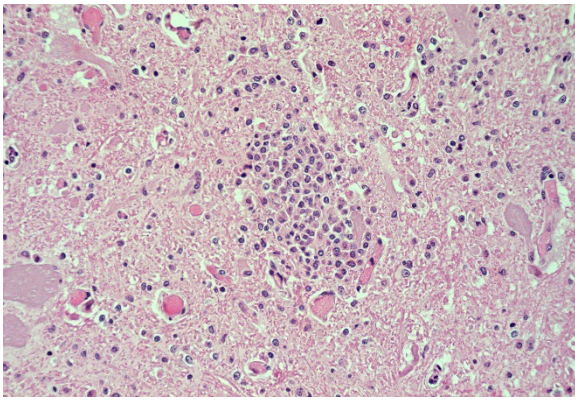

Figure 4-4: Cervical spinal cord, horse. Inflammatory infiltrates occasionally form discrete nodular aggregates adjacent to degenerating neurons in the gray matter (HE, 400X). (Photo courtesy of: Instituto Nacional de Investigación Agropecuaria (INIA), La Estanzuela, Uruguay. www.inia.uy

tral blindness, seizures, and terminal paralysis[14]. There are usually no gross changes, while histologic lesions frequently localize in the cerebral cortex and are almost limited to

the gray matter, typically with prominent neutrophil infiltration when the course is short or lymphoplasmacytic infiltration after a couple of days. Other common findings are neuronal degeneration, neuronophagia, gliosis, edema, and hemorrhage[4]. The histologic lesions caused by these three alphaviruses are similar in nature and distributions. For this reason, specific testing (i.e. PCR, IHC, ISH, and/or virus isolation) is required to confirm the etiologic diagnosis.

Outbreaks of arboviral-encephalitis usually affect non-vaccinated horses10. As vaccination is not mandatory in South America, many horses are not routinely vaccinated against these diseases.

Contributing Institution:
Instituto Nacional de Investigacion Agropecuaria (INIA), Uruguay. Avenida Italia 6201, Edificio Los Guayabos, Parque Technologico del LATU, Montevideo, Uruguay, www.inia.uy

JPC Diagnoses:
Cervical spinal cord: Poliomyelitis, lymphohistiocytic, diffuse, mild, with multifocal neuronal degeneration.

JPC Comment:
Last year's WSC coordinator, MAJ James Gaffney, adorned in a black cowboy hat provided by COL Daye for case presenters, grabbed this spinal cord case by the dorsal horns and proclaimed, "Pardner, this slide ain't big enough for the two of us." In the end, the slide was wrassled and conference participants branded this a "poliomyelitis" due to the focus of the inflammation being within the grey matter of the spinal cord. This case stimulated great discussion about the need for pathologists and clinicians alike to pay special attention to equine neurologic cases for which viral differentials are considered, as every virus on the differentials list is reportable and almost all are zoonotic. This list included flaviviruses (West Nile virus, Japanese encephalitis virus, Saint Louis encephalitis virus), the equine alphaviral encephalidities (WEEV, EEEV, and VEEV), equine herpesvirus-1, and

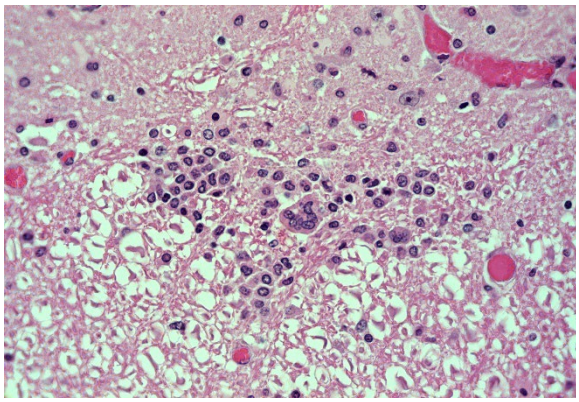

Figure 4-5: Cervical spinal cord, horse. Multinucleated cells interpreted as multinucleated astrocytes (center) occasionally admix with the inflammatory infiltrates in the gray-white matter junction. (HE, 400X). (Photo courtesy of: Instituto Nacional de Investigación Agropecuaria (INIA), La Estanzuela, Uruguay. www.inia.uy

rabies virus. In cases where any of these viral etiologies is suspected, rapid reporting and confirmatory diagnosis are crucial.

WEEV is widely considered to have arisen from a recombination event between Eastern equine encephalitis virus (EEEV) and a Sindbis-like alphavirus that resulted in a viral chimera. This recombinant virus ultimately diversified into WEEV, Highlands J Virus (HJV) and Fort Morgan virus (FMV), all of which are considered part of the WEEV antigenic complex. All three of these WEEV strains are considered endemic to North America2.

The first major outbreak of WEEV in the United States occurred in the 1940s with approximately 500,000 equine cases and several thousand human infections. The disease resurged with an additional outbreak in the United States and Canada the 1980s. Since then, cases in the United States have dropped significantly. However, Uruguay and Argentina experienced another outbreak of WEEV in 2024, with both equines and humans affected, bringing WEEV back to the forefront of disease surveillance.

WEEV causes disease through a variety of factors. Its structural proteins play significant roles in its survivability and pathogenesis and include a capsid protein, a signal peptide (E3), an envelope glycoprotein (E2) that binds target receptors, another envelope glycoprotein (E1) that primarily functions to fuse the virus with the cellular membrane of the target cell, and a signaling peptide (6K) that may also function as a viroporin6. These structural proteins continue to be targets in WEEV vaccine research.

Target cell receptors of WEEV have historically included protocadherin 10 (PCDH10), Very Low-Density Lipoprotein Receptor (VLDLR), and apolipoprotein E receptor 2 (ApoER2), all of which are expressed by neurons in the CNS7. However, the binding affinity for these receptors has changed significantly over time and has played a role in the submergence of WEEV in North America. A newer strain of WEEV has, for example, lost the ability to bind mammalian PCDH10, but continues to bind avian PCDH107. This changing affinity for receptors across species keeps those that study WEEV on their toes and provides a sentinel for potential re-emergence of WEEV.

Conference discussion touched on some of these evolutions as part of the viral ecology that led to the 2024 resurgence of WEEV in South America. Rapid genetic changes, in concert with increased rainfall leading to booming mosquito populations, bird migrations providing ample reservoirs, lower vaccination rates against WEEV in horses, and surveillance gaps due to the disease being considered historic in South America all likely

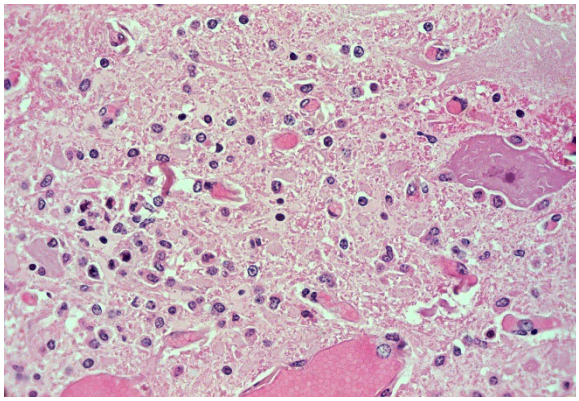

Figure 4-6: Cervical spinal cord, horse: The neuron to the right side of the image is shrunken, has angular cell borders and fading nucleus, and is surrounded by phagocytes that are in close contact to the cell body (satellitosis / early neuronophagia). There is increased cellularity due to inflammatory cell infiltration and gliosis in the adjacent neuropil. (HE, 400X). (Photo courtesy of: Instituto Nacional de Investigación Agropecuaria (INIA), La Estanzuela, Uruguay. www.inia.uy)

contributed to the outbreak and are a prime example of how rapidly deadly viruses can re-emerge in the face of ideal ecologic conditions.

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